Process Validation:
Successes and Failures on Inspection

WCBP 2005 January 10, 2005
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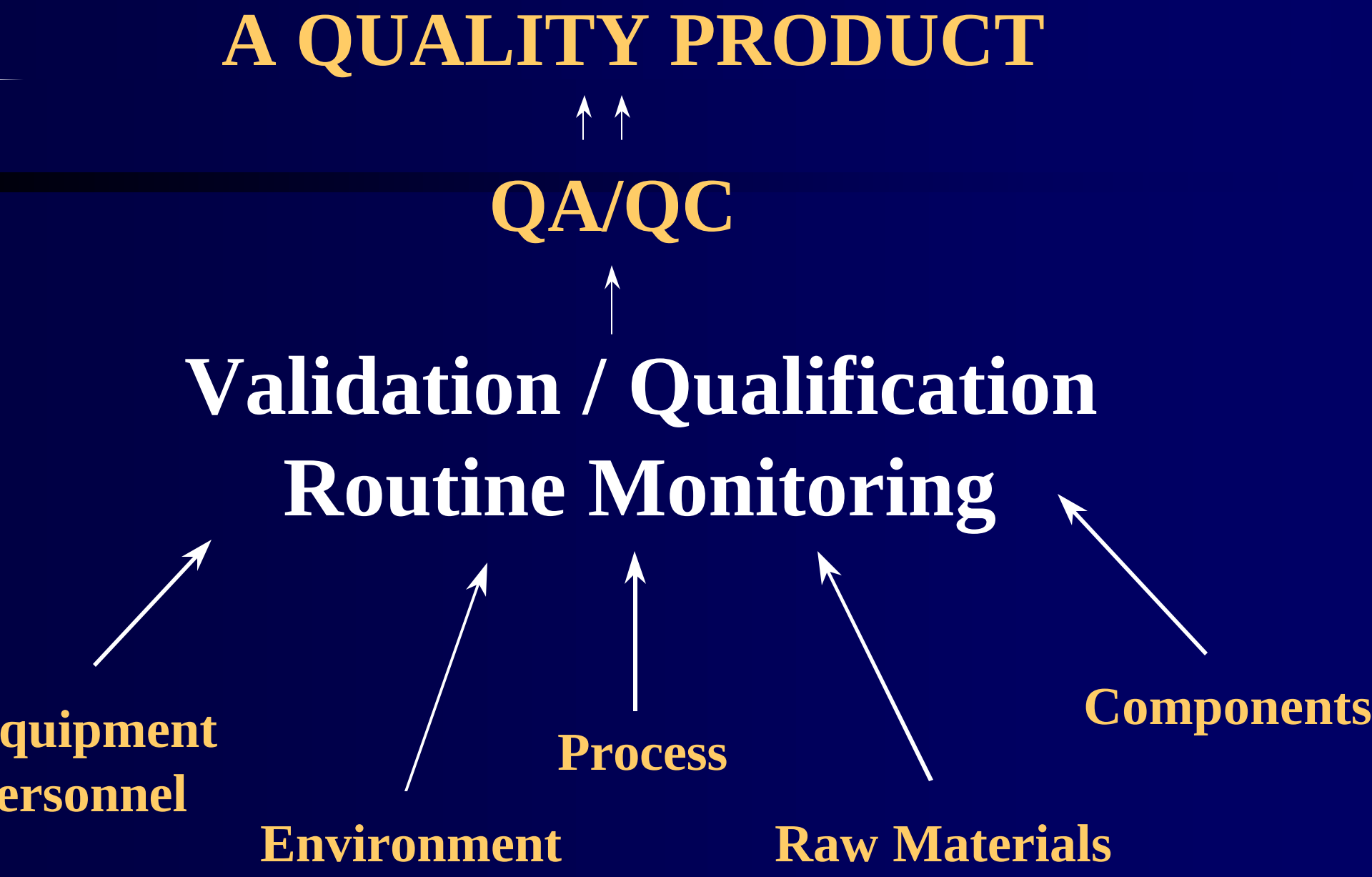
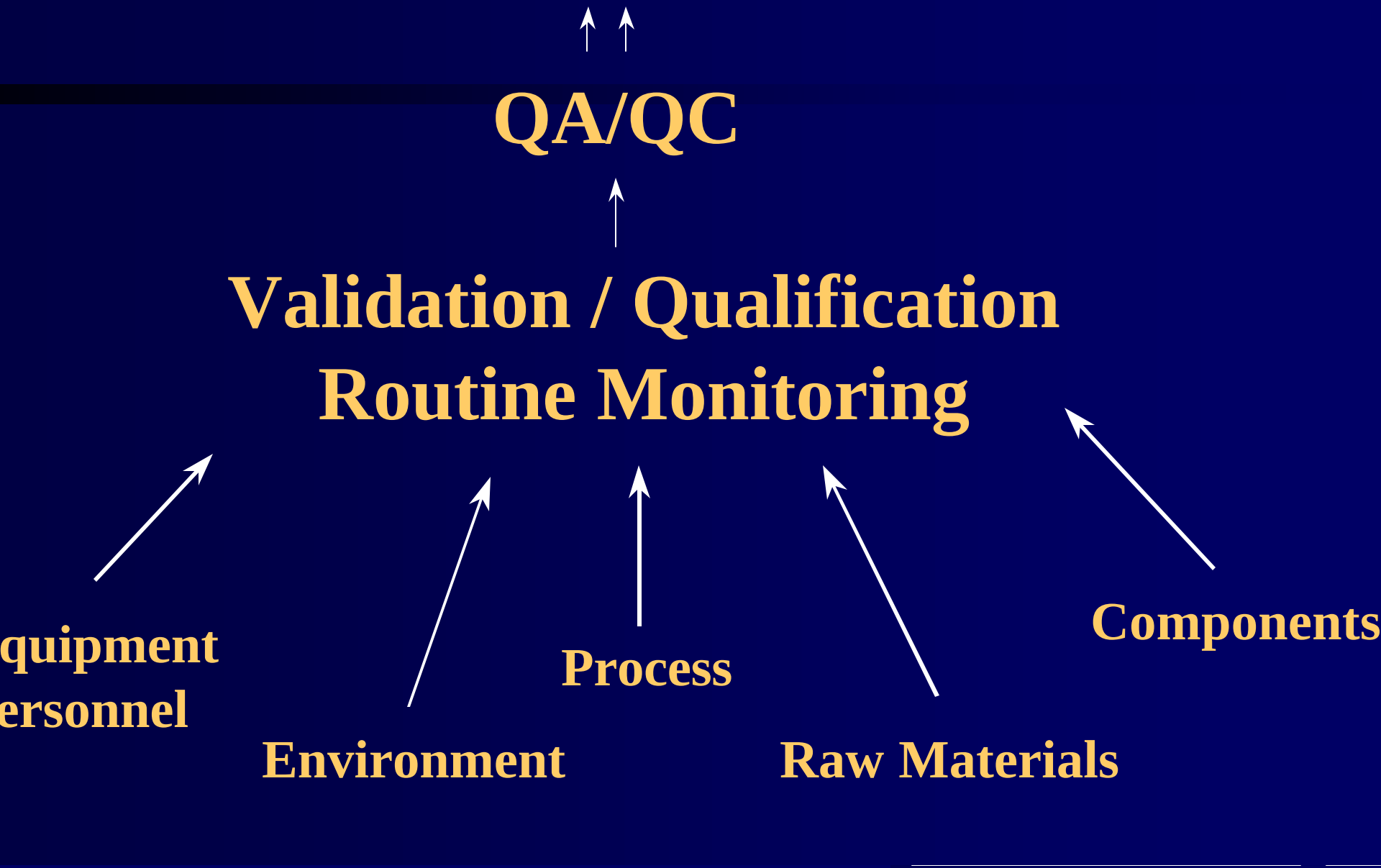
Acknowledgements

- OCBQ/Division of Manufacturing and Product Quality:
  - John Finkbohner, Ph.D.
  - Robert Darius
  - Dan Kearns
  - Robert Stevenson


A QUALITY PRODUCT
QA/QC
Validation / Qualification
Routine Monitoring
quipment
ersonnel
Environment
Process
Raw Materials
Components

A QUALITY PRODUCT



Process validation

- Developmental studies
- Proper identification of critical parameters
- Protocol development
- Execution – manufacture of conformance batches

Other factors

- ✓ Equipment - calibrated, qualified, compatible, cleaned (validated)
- ✓ Personnel – adequately trained, "ownership"
- ✓ Environment – qualified, maintained
- ✓ Raw Materials – qualified, consistent
- ✓ Components – qualified, consistent

Additional….

- ✓ Facility and systems – suitable, validated, sanitized (validated)
- ✓ Validated methods
- ✓ Contract activities?
- ✓ Quality Oversight
  - ✓EVERYWHERE

After the conformance lots…

- ✓ Routine monitoring of critical IPCs
- ✓ Routine monitoring of critical equipment parameters; preventive maintenance; calibration
- ✓ Routine monitoring of environment; personnel (as applicable)
- ✓ Ongoing training activities
- ✓ Quality Oversight

“Success consists of going from failure to failure without loss of enthusiasm.”

Winston Churchill

Failure to Success

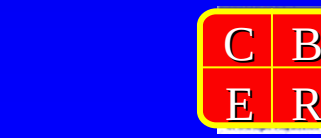
- Firm A cited for inadequate validation of its bulk lyophilization process:
  - Inconsistent production; failures or borderline failures for critical parameters
  - Appearance issues

Options?

- Option 1
  - Attempt to revalidate current cycle
- Option 2
  - Developmental studies to determine optimum cycle

Option 1

- Most commonly selected
- Why?
  - Less time investment
  - Less resource intensive
  - Economics
- Results?
  - Generally negative
  - “Still broke”



Option 2

- Firm A selected option 2
  - Modernized and requalified equipment
  - Developmental work resulting in optimized cycle
  - Took more time, resources, money

Results?

- Critical process parameters consistently met; appearance issues resolved; no rejected batches

+

- Cycle time reduced >1/2; more throughput; economic benefits
- Increase in yield; economic benefits =

Public Health benefits

“Success is relative. It is what we can make of the mess we have made of things.”

TS Eliot

Success to Failure to…

- Firm B appeared to do everything correctly
  - Qualified equipment/cleaning validation
  - Adequate number of trained personnel
  - Maintenance of proper environment
  - Use of consistent, quality raw materials and components
  - Solid developmental work; successful conformance batches

One year later……

- Upward trend in bioburden after specific manufacturing step
- Eventual failures due to high bioburden
- Production stopped while thorough investigation undertaken

Result?

- Lack of proper identification of critical equipment controls after validation + lack of compatibility assessment of equipment with product and cleaning solutions = pinhole leaks between jacket and equipment and subsequent contamination of process stream went undetected until out of control.

Result?

- Large resource and economic investment to identify and correct problem
- Time off the market = detrimental to the Public Health

“Failure is the opportunity to begin again, more intelligently.”

Henry Ford

Success (Almost)

- Firm C installs new filling line (isolator technology).
  - Extensive qualification work
  - Extensive validation work including worst-case challenges
  - Controls appropriately set

During the PAI…

- Equipment controls not adhered to.
- Preventive maintenance program already delinquent
- During production, personnel had difficulty with manipulation using isolator gloves

Problem??

- Inadequately trained personnel
  - Not following procedures
  - Hands on training questionable
- First line management unsure of responsibilities
- No involvement by operators or supervisors in validation activities; including procedural development – no ownership

“I have not failed. I have just found 10,000 ways that won’t work.”

Thomas Edison

Success

- Firm D:
  - ✓Well understood process at current scale
  - ✓Scale up carefully planned
  - ✓Adherence to all “important factors” during routine production and scale up activities

Success

- Pre-submission meeting with FDA
- Comparability protocol submitted and approved (not intended to downgrade)
- Submission of extensive developmental data
- Rationale for critical and non-critical parameters clearly tied to developmental data

Success

- Successful execution of comparability protocol
- Preapproval inspection – no surprises/problems
- Approval followed by successful commercialization of scaled-up process

Other common process validation related inspectional issues…….

Process related

- Hold steps validated and documented?
- Upper and lower limits for operating parameters?
  - E.g. time, speed
- Purification Columns adequately controlled?
- Conformance lots produced using process submitted in application?
- IPC supported by production data?
- Any rework/reprocessing steps validated?

Equipment Related

- Has each unit operation been assessed for suitability/compatibility of equipment with product and cleaning solutions?
- Has equipment cleaning been adequately validated?

Personnel Related

- Gowning practices appropriate?
- Adequate training?
- Manufacturing supervisors appropriately experienced with the process?
- Quality approach to all operations?

Environment Related

- Are controlled production environments appropriately qualified and monitored for HVAC system performance and microbiological quality?
- Monitoring systems adequate for open product manipulations and aseptic operations?

Raw Materials Related

- Incoming material sampling plans appropriate?
- Acceptance criteria supported?
- Quarantine/release procedures appropriate?

Component Related

- Suppliers adequately qualified?
- Acceptance activities appropriate?
- Compatibility/extractable studies performed?

“The dictionary is the only place where success comes before work.”

Vince Lombardi